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# Pharmaceutical Applications of Polymorphism

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**Keyphrases** ☐ Polymorphism—pharmaceutical applications ☐ Stability, chemical—polymorphorphism ☐ Methodology—polymorphism determination ☐ Metastable polymorphs—preparation

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state. The molecule itself may be of different shape in the two polymorphs, but that is not necessary and, indeed, certain changes in shape (involving dynamic isomerism or tautomerism) involve formation of different molecules and hence do not constitute polymorphism. Geometrical isomers or tautomers, even though interconvertible and reversibly so, cannot be called polymorphs although they may behave in a confusingly similar manner. Shape changes, permissible in the molecule crystallizing in two or more polymorphic forms, include resonance structures, rotation of parts of the molecule about certain bonds, and minor distortions of bond distances and angles. These distortions of molecular shape result from polarizability effects of one molecule on another due to the change in relative positions of adjacent molecules in the two different crystalline arrangements.

A safe criterion for classification of a system as polymorphic is the following. Two polymorphs will be different in crystal structure but identical in the liquid and vapor states. Dynamic isomers will melt at different temperatures, as do polymorphs, but will give melts of different composition. In time each of these melts changes to an equilibrium mixture of the two isomers with temperature-dependent composition. Some reported cases of polymorphism are undoubtedly dynamic isomerism, since the two behave quite similarly, especially if the equilibrium between the two isomers is very rapidly established.

Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species (*e.g.*, carbon as cubic diamond or hexagonal graphite). Different polymorphs of a given compound are, in general, as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, *etc.*, all vary with the polymorphic form. In general, it should be possible to obtain different crystal forms of a drug and thus modify the performance properties for that compound. To do so requires a knowledge of the behavior of polymorphs.

Mitscherlich (1) is generally given credit for first using the term polymorphism during his work on the isomorphous sulfates of iron (ferrous), cobalt, nickel, magnesium, copper, zinc, and manganese. It is, however, obvious that the idea was not new at that time, since Humphrey Davy in 1809 pointed out that diamond and graphite are both carbon and that the two differ only in their arrangement of carbon atoms in the solid phase. Indeed, Klaproth may have been the first to be aware of polymorphism when he observed (1788) that calcium carbonate crystallizes both as calcite and as aragonite.

Since that time a very large number of compounds, organic and inorganic, as well as the elements themselves, have been shown to crystallize in two or more different crystalline arrangements—chemically identical, physically different. Besides graphite and diamond there are, to name a few in the mineral field, wurtzite and sphalerite (ZnS); calcite, aragonite, and vaterite ($CaCO_3$); rutile, brookite, and anatase ($TiO_2$). Most polymorphs, especially those of organic compounds, do not have special names; instead they are referred to as $\alpha$,

**Table VII**—Comparison of *In Vitro* and *In Vivo* Dissolution Rates and Adrenal Cortex Atrophy

| Phase | *In Vitro* Dissolution Rate at 23°C. and 6 r.p.m. (mg./cm.²/hr.) | Ratio[a] | *In Vivo* Dissolution Rate (mg./cm.²/hr.) | Ratio | Adrenal Cortex Atrophy (g. Atrophy/g. of Rat wt./hr. × $10^{-7}$) | Ratio |
|---|---|---|---|---|---|---|
| Form I | 0.917 | 2.24 | 0.237 | 1.61 | 8.05 | 1.46 |
| Form III | 0.804 | 1.96 | 0.209 | 1.42 | 7.09 | 1.28 |
| Form II | 0.571 | 1.39 | 0.186 | 1.26 | 6.57 | 1.19 |
| β-Monohydrate | 0.527 | 1.29 | 0.162[b] | 1.10 | 6.11 | 1.11 |
| α-Monohydrate | 0.410 | 1.00 | 0.147[b] | 1.00 | 5.52 | 1.00 |

[a] Compared to α-monohydrate. [b] Corrected for *in vivo* dissolution rate of anhydrous fluprednisolone.

dissolved in the gastric fluids, the *in vivo* dissolution rate of aspirin in tablet form in the stomach would be reflected. It is possible that polymorphism may also be involved with availability from commercial aspirin tablets. Tawashi (44) has reported on the dissolution of two polymorphic forms of aspirin where Form II dissolves 50% faster than Form I. Ballard and Nelson (36) have investigated the absorption rate of pellets after subcutaneous implantation. Their absorption data on anhydrous tetracycline pellets were anomalous since the mean weight after implantation was greater than before. They observed, "The increase in mean weight could not be explained on the basis of 'ghost' formation. The increase in weight could be satisfactorily explained assuming that the anhydrous tetracycline was converted to the trihydrate in the body. Thus, the weight loss of the pellets due to absorption was more than compensated for by the increase in molecular weight due to hydration."

### Polymorphism and Tableting Behavior of Powders

Shell (45) described the use of different habits of the same compound and their effects on tableting behavior. (The outer appearance of a crystal is its habit while polymorphism is a function of the internal structure of crystals.)[1] Shell found that the ease or difficulty of tableting a powder where the active ingredient makes up a large portion is due mostly to "anisotropy of cohesion and of hardness which is possessed by organic crystals and, therefore, of most pharmaceutically important compounds" (45).

According to Shell (47), polymorphs of the same compound, which can crystallize in different habits, when forming a large portion of the tableting mixture, can exhibit similar problems. The choice of the right polymorph, all other conditions being equal, will be the one with a habit which can be tableted easily.

### Miscellaneous Applications of Polymorphism

One other potential application of polymorphism which could be used in the pharmaceutical industry is preparation of fine particles, about micron size, by using the density difference for enantiotropic polymorphs.

Different polymorphs of the same compound have different densities. Due to this phenomenon, when one polymorph is heated above its conversion temperature to another polymorph, and then cooled to room temperature, strains can develop in the crystal and produce fracturing into finer particles. This type of operation would require existence of suitable polymorphic forms and that the repeated temperature cycling would not produce chemical degradation. This mechanism of particle size reduction, in certain instances, might prove to be more efficient than present methods of micronization.

Hsiachen and Grabar (48) reported on a novel effect of polymorphism in solid-state polymerization. They found that tributylvinylphosphonium bromide exists in three phases. Of these, Phase II is a metastable phase, and it polymerizes faster than the other phases, which is due to steric and collision factors which are governed by crystalline structure.

### Methods Used to Study Polymorphism

A number of techniques have been used to identify different polymorphic phases of a compound. Each of these techniques could be successful in identifying the phase, but a combination of methods provide a powerful means for identification and isolation of each crystalline modification (49).

**Microscopy**—*Optical Crystallography*—Biles (50) in his review of crystallography has discussed optical crystallography and its application to identification of polymorphs. Different polymorphs of a crystal may belong to one of two classes depending on the effect of the transmission of light in different directions through the crystals. These are isotropic and anisotropic classes. In the isotropic crystals the velocity of light, or the refractive index which depends on the velocity of light, is the same in all directions, and in the anisotropic crystals there may be two or three different light velocities or refractive indices. Different polymorphs having dif-

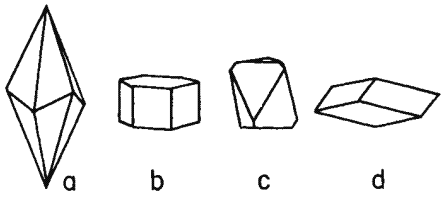


**Figure 7**—*Crystal habits of calcite.*

[1] A good example in differentiating polymorphism and habit is $CaCO_3$. Calcite, one of the polymorphs of $CaCO_3$, crystallizes in the trigonal system and shows 4 different habits as seen in Fig. 7 (46), where each of these habits belong to the same crystal class and are developed upon the same internal structure. While aragonite, the other polymorph of $CaCO_3$ is orthorhombic and does not have the same internal structure.

ferent internal structures will belong to different crystal systems and have different sets of refractive indices. Biles (49) reported the optical crystallographic properties of some polymorphs of prednisolone and hydrocortisone *tert*-butyl acetate, while Trivedi *et al.* (51) reported the optical crystallographic properties of ouabain hydrates. Eisenberg (52) compiled the optical crystallographic characteristics of some NF drugs exhibiting polymorphism.

*Hot Stage Methods*—The polarizing microscope fitted with a hot stage (or cold stage) is a very useful tool for investigating polymorphism. With this combination an experienced microscopist can quickly tell (*a*) whether polymorphism exists; (*b*) the degree of stability of the metastable forms; (*c*) transition temperatures and melting points; (*d*) rates of transition under all temperature and physical conditions; (*e*) whether to pursue polymorphism as a route to an improved dosage form. These methods are discussed in detail by the Koflers (5) and by McCrone (6, 53).

**X-Ray Powder Diffraction**—Crystalline materials in powder form give characteristic X-ray diffraction patterns made up of peaks in certain positions and varying intensities. From the $2\theta$ values of these peaks, the spacing values ($d$ distance) for the different planes of the crystal can be calculated using the Bragg equation, $n\lambda = 2d \sin \theta$, where the wavelength of the X-ray source is known. Each powder pattern of the crystal lattice is characteristic for a given polymorph. X-ray powder diffraction has the advantage over other identification techniques in that the sample is examined as presented (after size reduction), very small amounts of samples are needed, and the sample can be recovered since the method is nondestructive. Since the diffraction peaks are additive for mixtures of compounds care must be taken to insure that the samples do not contain impurities. X-ray powder diffraction is one of the most widely used techniques after optical microscopy. Several investigations have used this method to identify polymorphs of pharmaceuticals (20, 49, 51, 54–56).

**Infrared Spectroscopy**—In identification of different polymorphs with IR spectroscopy only solid samples (as mineral oil mulls or potassium bromide pellets) can be used, since in solution polymorphs of a compound have identical spectra. Many authors (18, 20, 54, 57, 58) have used IR spectroscopy to study polymorphism. Kendall (57) claimed that, in addition to being rapid, the technique is both quantitative and qualitative. Smakula *et al* (59) reported that when different polymorphs of estradiol-17$\beta$ were triturated as a mull for different time intervals the IR absorption spectra for these phases were changed to a common spectrum.

**Differential Thermal Analysis**—In differential thermal analysis (DTA), heat loss or gain resulting from physical or chemical changes occurring in a sample is recorded as a function of temperature as the substance is heated at a uniform rate. Enthalpic changes, both exo- and endothermic, are caused by phase transitions. For example fusion, boiling, sublimation, vaporization, crystalline structure inversion, solid-solid transition, and water loss generally produce endothermic effects,

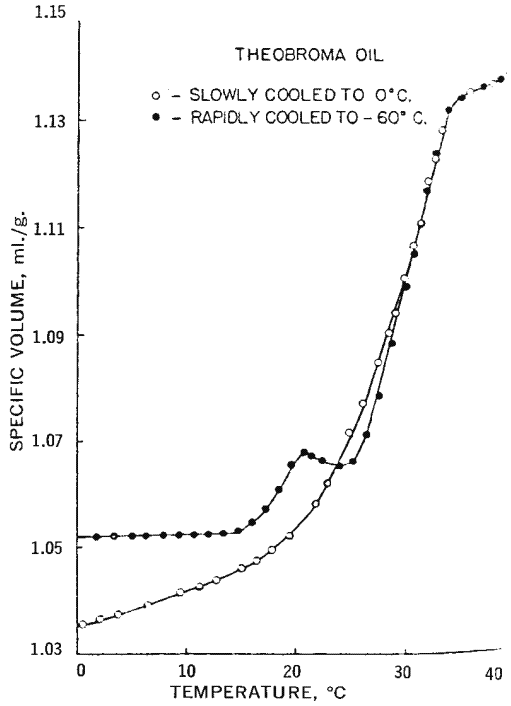


**Figure 8**—*Dilatometric curves, theobroma oil, slowly and rapidly cooled.*

whereas crystallization produces exothermic effects (60). One of the advantages of DTA is the ability to calculate the heats of transition from one polymorph to the other. Guillory (61) using DTA, obtained the heats of transition of methyl prednisolone and sulfathiazole polymorphs.

**Dilatometry**—Dilatometry is the measurement of changes of volume caused by thermal or chemical effects. Ravin and Higuchi (62), using dilatometry, followed the melting behavior of theobroma oil by measuring the specific volume of both rapidly and slowly cooled theobroma oil as a function of bath temperature (Fig. 8). The sample which was slowly cooled exhibited no unusual behavior, while the sample rapidly cooled showed an expansion behavior between 16 and 20° followed by a contraction between 20 and 24°. The authors suggested that this was probably due to an unstable modification, and the expansion followed by contraction resulted from the phase conversion from a less dense unstable form to a more dense stable form.

**Proton Magnetic Resonance Spectroscopy**—Chapman *et al.* (55) working with water-soluble compounds such as cephaloridine found that the combination of solid-state IR with proton magnetic resonance (PMR) measurements on heavy water solutions provided a test for polymorphism. In this method, the crystalline form is distinguished by solid state infrared and the chemical identity by PMR measurements on heavy water solutions. The PMR measurements not only confirm the structure but also yield quantitative information on solvent and other impurities, which could be very helpful in establishing the number of moles of solvent solvated with the compound under study.

**Nuclear Magnetic Resonance Spectroscopy**—Rudman and Post (63) investigated the NMR spectrum of cyclooctanone over the temperature range −120 to +25° and

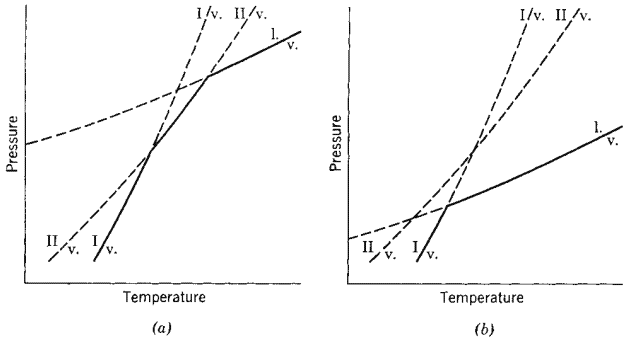


**Figure 9**—*Sublimation and boiling point curves for* (a) *enantiotropic system and* (b) *monotropic system.*

found that cyclooctanone forms three distinct crystalline phases in the temperature range investigated. The results were also verified by X-ray diffraction and differential thermal analysis.

**Electron Microscopy**—Hamm and Norman (64) in their work with organic pigments observed that both copper phthalocyanine and indanthrene blue RS can exist as crystals of varying shades. These shade differences are the result of differences in the light absorption exhibited by the polymorphic phases. They reported that the polymorphic transformations can be readily observed to take place in the electron microscope. It was found that the new forms of both pigments, completely stable to the illuminating beam after the transformation, can be seen to grow from the vapor state at the expense of the original metastable material.

The polymorphic transformations, especially in colored compounds, are almost invariably accompanied by changes in color. This is expected because the true "body" color of a solid is determined by its crystal structure as well as by its chemical chromophoric groups.

**Magnetic Anisotropy**—Cini *et al.* (65) identified different polymorphs of $NH_4NO_3$, $KNO_3$, $TlNO_3$, and $AgNO_3$ by following, at different temperatures, the variation of magnetic anisotropy of a powdered sample contained in a spherical container which is suspended by a torsion wire in a uniform magnetic field.

As the temperature is raised a sharp break of magnetic anisotropy occurs at the transition point of each compound ($NH_4NO_3$, 35, 86, and 127°; $KNO_3$, 127.5°; $TlNO_3$, 77.5 and 147°; and $AgNO_3$, 160°).

## Study of Polymorphism

The polarizing microscope is, by far, the favored tool for the study of polymorphism (7, 53, 66-68). X-ray diffraction is also useful but the others listed are most useful for routine quality control, *e.g.*, DTA, or for elucidation of molecular differences between polymorphs, *e.g.*, NMR. Most of the rest of this paper will deal with microscopical methods.

The complete characterization of a compound should include a complete phase diagram, preferably plotted as a solubility-temperature diagram, and composition diagrams for all solid phases of the drug with all other components of the formulation. Some of the questions the investigator must be able to answer include:

1. How many polymorphic forms exist?
2. How stable are the metastable forms, and what are the relative degrees of stability for all of the polymorphic forms?
3. Is there a noncrystalline glass state and is it stable enough to consider as a dosage form?
4. Can any metastable forms be stabilized?
5. What are the temperature stability ranges for each crystal form?
6. What are the solubilities of each form?
7. How can pure and stable crystals of each form be prepared?
8. Will the more soluble metastable form survive processing, *e.g.*, micronizing or tableting?
9. Does the drug react with any other chemical component during processing or final formulation to form a molecular addition compound?
10. If so, what are its physical properties, *e.g.*, stability, solubility, and melting point, and can it exist in a desirable metastable polymorphic form or glass?

**Phase Diagram**—Before suggesting ways of answering some of the practical questions regarding polymorphism, it is worthwhile to review the types of phase diagrams shown by systems involving polymorphs (7). This will be done first for a simple example of a system of two forms only. There will be only one liquid-vapor (boiling point) curve in the pressure-temperature diagram, since both polymorphs give identical liquid phases on melting. Each polymorph, moreover, has its own solid-vapor (sublimation or vapor pressure) curve (Fig. 9) and its own solid-melt (melting point) curve. The complete diagram, or course, contains the melt-vapor, the solid-vapor, and the solid-melt curves (Fig. 10), and these can intersect to give either of two general possibilities, the melt-vapor curve may intersect the two solid-vapor curves above or below their intersection. It is not unknown for the three curves to intersect at the same point. When this occurs, the melting points of the two polymorphic forms and the transi-

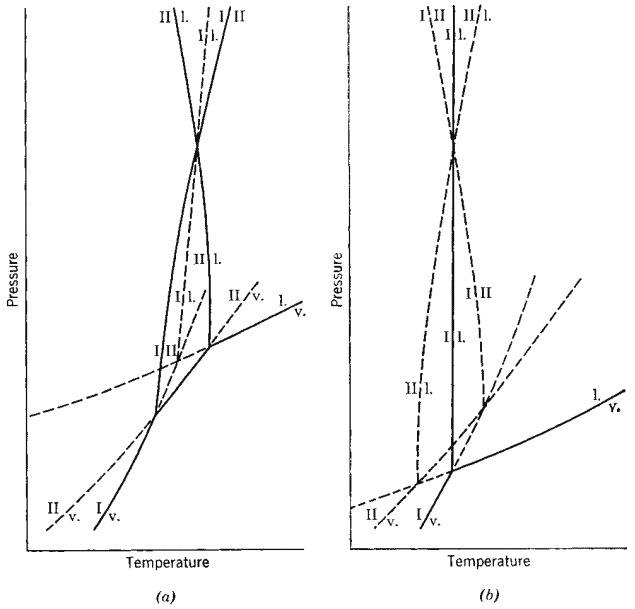


**Figure 10**—*Melting point and transition temperature curves added to the curves in Fig. 9;* (a) *enantiotropic* (b) *monotropic.*